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I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003906117 for a patent by CHEMEQ LTD as filed on 06 November 2003.



WITNESS my hand this  
Nineteenth day of November 2004

A handwritten signature in black ink, appearing to be "dA".

LEANNE MYNOTT  
MANAGER EXAMINATION SUPPORT  
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**AUSTRALIA**  
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**PROVISIONAL SPECIFICATION**

Invention Title:   Method of Manufacture of Polyacrolein

Applicant:       **Chemeq Ltd**

The invention is described in the following statement:

## METHOD OF MANUFACTURE OF POLYACROLEIN

This invention relates to a method of manufacture of polyacrolein and, in particular, to a method of manufacture of polyacrolein for use in antimicrobial compositions.

The use of polyacrolein in antimicrobial applications has been described in U.S. Patent 5,290,894, in our International patent publication WO 96/38186 (PCT/AU96/00328) and more recently we have described a method of improving the activity of acrolein polymers in our International patent publication WO 01/60874 (PCT/AU00/00107).

Many of the most stable compositions of polyacrolein for use as antimicrobials are formed by subjecting the polymer to an oxidation step which results in the formation of carboxylic acid groups. The presence of carboxylic acid groups has been found by us to improve the solubility of polyacrolein compositions. We have now found that polyacrolein polymers of high solubility, microbiological activity and stability may be formed without the requirement for this aerial oxidation step.

Accordingly, the present invention provides a method of manufacture of soluble, microbiologically active and stable polyacrolein comprising : (a) polymerising acrolein by anionic polymerisation to form a polymer of acrolein; (b) dissolving the polymer of acrolein in an alcohol selected from monoalcohols and polyols optionally with addition of water; (c) heating the alcohol solution of acrolein to form acetal derivatives thereof; and (d) adding base to the composition.

It will be apparent to those skilled in the art that a co-monomer, especially a water-soluble or latently water-soluble co-monomer may be used in step A. Typically when a co-monomer is used it will constitute less than 10% by weight of the total monomer composition. We prefer that the acrolein polymer is a homopolymer.

- The polyacrolein used in the method of the invention is formed by anionic polymerisation of acrolein monomer. Polymerisation is generally conducted in an alkaline solution and the acrolein polymer may be collected as a precipitate. The precipitate may, in the process of the invention, be dissolved in the alcohol
- 5 without a requirement for prior oxidation, brought about by heating in air or oxygen, to form poly(2-propenal, 2-propenoic acid). The acrolein homopolymer will generally be isolated from the polymerisation reaction and is preferably reacted with the alcohol in a solution of pH of no more than 7.
- 10 The precipitate formed in the preferred aspect of the invention may be dissolved in the alcohol without needing to further process it. This is an advantage over processes requiring oxidation of the precipitation as this step may be time consuming or include milling or grinding to improve the rate of oxidation.
- 15 In the process of the invention, the polyacrolein homopolymer is dissolved in the alcohol. This process would generally involve heating the polyacrolein in the alcohol to a temperature in the range of from 40 to 90°C. The preferred alcohol is a polyalkylene glycol and, most preferably, is a polyethylene glycol of molecular weight in the range of from 200 to 2,000. The polyacrolein
- 20 homopolymer is heated in the alcohol to form an acetal derivative of the polyacrolein. Typically, the alcohol solution will be heated for a period in the range of from fifteen minutes to five hours with the alcohol and at a temperature in the range from 50 to 90°C, more preferably from 60 to 90°C.
- 25 Generally, the polyacrolein formed in step (a) used in the process of the invention will have a low acid content typically of less than 1 mole of carboxyl groups per kg of polymer and most preferably less than 0.5 mole acid groups per kilogram of polymer. Despite the low content of carboxyl groups, we have found that when the polymer is heated in the alcohol to form acetal groups and
- 30 the alkali is added, the alkaline solution resists precipitation when diluted with water, which would not have been expected for an unoxidized polymer.

The process of the invention includes a step of adding base to the composition, the base is generally added to the alcohol solution following formation of

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acetals. The pH of the resulting solution of acetal derivative is preferably in the range of from 7 to 9.5 and more preferably is from 7.5 to 8.5. The preferred base for addition to the alcohol solution of polyacrolein is an alkali metal carbonate particularly sodium carbonate or potassium carbonate. Alkaline metal hydroxide such as sodium hydroxide or potassium hydroxide may also be used but are less preferred. Typically the alkali is added as an aqueous solution. Preferably the solution is cooled to room temperature before adding the base in the above step.

- 10 The concentration of homopolymer used in the step of forming acetals is generally from 0.5 to 50% by weight and more preferably from 0.5 to 40% by weight. The alcohol such as polyethylene glycol will preferably constituted from 50 to 90% by weight. The polyacrolein prepared by the method of the invention is useful in a range of applications, especially antimicrobial. The preferred applications include antiseptic compositions and compositions for use in treatment of gastrointestinal disease. The compositions formed in accordance with the invention generally have a good long-term antimicrobial activity. Typically, the acrolein polymers provided by the method of manufacture described above will provide a minimum kill concentration of less than 150 ppm against a range of bacteria, e.g. *E. coli*, at  $10^4$ - $10^9$  cfu/mL, after storage at 40°C for no less than twenty days.

25 The composition prepared by the method of the invention is particularly suited to use in administration of animals for treatment or prophylaxis of gastrointestinal disease, particularly gastrointestinal microbial infection. The composition prepared by the method of the invention may be administered to animals via drinking water, via food or other suitable means such as tablets, syrups and the like.

- 30 The invention will now be described with reference to the following examples. It is to be understood that the examples are provided by way of illustration of the invention and that they are in no way limited to the scope of the invention.

## Examples

### Biocidal test method

- 5 The following method was used for biocidal testing in the examples.

10 Dissolve sample with 1% by weight aqueous sodium bicarbonate to obtain the required concentration (unless specified to the contrary, 0.125% by weight of polymer). Weigh 19.9g of diluted sample into a sterile jar and inoculate with 0.1 mL of 107-108 cfu of *Ps.aeruginosa* and mix. At specified time-intervals, transfer 1 mL of inoculated sample to 9 mL of Letheen broth and vortex. Plate out serial 1 in 10 dilutions. Pour with trypticase soy agar. Incubate 3 days at 37°C.

15 Example 1 – Preparation of Polyacrolein

Water (720 mL at ambient temperature, about 20°C) and acrolein (60g; freshly distilled, plus optionally hydroquinone added to 0.25%w/w) were placed in an open beaker, within a fume cupboard, and very vigorously stirred, mechanically. Then, 0.2 M aqueous sodium hydroxide (21.4 mL) was added to bring the pH to 10.5 - 11.0. The solution immediately turned a yellow typical of the hydroquinone anion and within a minute, the colour had disappeared and the clear solution became milky. About 1 minute later, precipitation of a white, flocculent polymer began, and appeared complete within 15-30 minutes. The precipitate was filtered and washed with water.

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### Example 2

Polyacrolein (5.0 g) was added to hot PEG-200 (64.0 g, 65 C) and the mixture stirred until the solid dissolved (20 min).  $\text{Na}_2\text{CO}_{3(\text{aq})}$  solution) (31 g of 1.29% w/w) was then added and the mixture heated at 65 C for 10 min. The mixture was then allowed to cool and the sample made up with water to 100 g to give a solution 5% w/w in polyacrolein. The pH of the neat solution was tested with PANPEHA pH sticks and the pH of a 1.0 g sample, diluted with water to 10 g total mass, was tested using a pH probe. The minimum-kill-concentration (MKC) was tested against *E.coli*.

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Example 3

50.1 grams of the solution from Example 3 was then heated at 90 C for 2 hours. The mixture was then allowed to cool and the sample made up with water to 50 g to give a solution 5% w/w in polyacrolein. The pH of the neat solution was tested with PANPEHA pH sticks and the pH of a 1.0 g sample, diluted with water to 10 g total mass, was tested using a pH probe. The minimum-kill-concentration (MKC) was tested against *E.coli*.

Example 4

10 Polyacrolein (5.0 g) was added to hot PEG-200 (64.0 g, 65 C) and the mixture stirred until the solid dissolved (5 min).. Water (25.0 g) was then added and the mixture heated at 105 C for hours. The mixture was then allowed to cool and the sample made up with water (a portion of which contained Na<sub>2</sub>CO<sub>3</sub> (0.40 g)) to 100 g to give a solution 5% w/w in polyacrolein. The pH of the neat solution was tested with PANPEHA pH sticks and the pH of a 1.0 g sample, diluted with water to 10 g total mass, was tested using a pH probe. The minimum-kill-concentration (MKC) was tested against *E.coli*.

Example 5

20 Polyacrolein (5.0 g) was added to hot PEG-200 (64.0 g, 65 C) and the mixture stirred until the solid dissolved (10 min). Water (26.0 g) was then added and the mixture heated at 90 C for 2 hours. The mixture was then allowed to cool and the sample made up with water (a portion of which contained Na<sub>2</sub>CO<sub>3</sub> (0.40 g)) to 100 g to give a solution 5% w/w in polyacrolein. The pH of the neat solution was tested with PANPEHA pH sticks and the pH of a 1.0 g sample, diluted with water to 10 g total mass, was tested using a pH probe. The minimum-kill-concentration (MKC) was tested against *E.coli*.

Example 6

30 Polyacrolein (5.0 g) was added to hot PEG-200 (64.1 g, 65 C) and the mixture stirred until the solid dissolved (5 min). Water (24.6 g) was then added and the mixture heated at 105 C for 4 hours. The mixture was then allowed to cool and the sample made up with water (a portion of which contained Na<sub>2</sub>CO<sub>3</sub> (0.40 g)) to 100 g to give a solution 5% w/w in polyacrolein. The pH of the neat solution

was tested with PANPEHA pH sticks and the pH of a 1.0 g sample, diluted with water to 10 g total mass, was tested using a pH probe. The minimum-kill-concentration (MKC) was tested against *E.coli*.

5    Example 7

Polyacrolein (1.0 g) was added to hot PEG-200 (12.8 g, 65 C) and the mixture stirred until the solid dissolved (5 min). Water (5.2 g) was then added and the mixture heated at 90 C for 0.5 hours then at 105 C for 2 hours. The mixture was then allowed to cool and the sample made up with water (a portion of which contained Na<sub>2</sub>CO<sub>3</sub> (0.04 g)) to 20 g to give a solution 5% w/w in polyacrolein. The pH of the neat solution was tested with PANPEHA pH sticks and the pH of a 1.0 g sample, diluted with water to 10 g total mass, was tested using a pH probe. The minimum-kill-concentration (MKC) was tested against *E.coli*.

15    Example 8

Polyacrolein (5.0 g) was added to hot PEG-200 (64.0 g, 65 C) and the mixture stirred until the solid dissolved (10 min). Water (20.0 g) was then added and the mixture heated at 90 C for 2 hours. The mixture was then allowed to cool and the sample made up with water (a portion of which contained Na<sub>2</sub>CO<sub>3</sub> (0.40 g)) to 100 g to give a solution 5% w/w in polyacrolein. The pH of the neat solution was tested with PANPEHA pH sticks and the pH of a 1.0 g sample, diluted with water to 10 g total mass, was tested using a pH probe. The minimum-kill-concentration (MKC) was tested against *E.coli*.

25    Example 9

Polyacrolein (5.0 g) was added to hot PEG-200 (64.0 g, 65 C) and the mixture stirred until the solid dissolved (10 min). Water (20.0 g) was then added and the mixture heated at 90 C for 2 hours. The mixture was then allowed to cool and the sample made up with water (a portion of which contained Na<sub>2</sub>CO<sub>3</sub> (0.40 g)) to 100 g to give a solution 5% w/w in polyacrolein. The pH of the neat solution was tested with PANPEHA pH sticks and the pH of a 1.0 g sample, diluted with water to 10 g total mass, was tested using a pH probe. The minimum-kill-concentration (MKC) was tested against *E.coli*.

**Table 1**

Sample (or)	Temp of dissolution	Add water	Add $\text{Na}_2\text{CO}_{3(\text{aq})}$	Time & Temp of 2 <sup>nd</sup> Heating	Add $\text{Na}_2\text{CO}_{3(\text{aq})}$	Colour	pH of neat solution	pH of 1-in-10 dilution	MKC
Example 2	65°C		5A (0.4%)	10 min @ 65°C		yellow/orange	8.5	6.85	31 ppm
Example 3	65°C		5A (0.4%)	2 h @ 90°C		orange	7.0	6.62	62 ppm
Example 4	65°C	5A		2 h @ 105°C	5A (0.4%)	brown	8.0	7.12	31 ppm
Example 5	65°C	5A		2 h @ 90°C	5A (0.4%)	brown	8.0	7.11	62 ppm
Example 6	65°C	5A		4 h @ 105°C	5A (0.4%)	brown	8.0	7.23	62 ppm
Example 7	65°C	5A		2 h @ 105°C	5A (0.2%)	brown	5.0	5.06	125 ppm
Example 8	65°C	5A		2 h @ 90°C	5A (0.4%)	brown	8.0	7.51	62 ppm
Example 9	65°C	5A		2 h @ 90°C	5A (0.4%)	brown	8.5	8.69	125 ppm

**Table 2 Stability Data for Example 5**

Sample	MKC	days at r.t.	MKC	days at 40 °C	Biocidal	days at r.t.	MKC	days at 40 °C	Biocidal	days at 40 °C
Example 5	62 ppm	2	31 ppm	17	Pass	31	62	52	Pass	59

DATED: 6 November, 2003

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# Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/AU04/001537

International filing date: 05 November 2004 (05.11.2004)

Document type: Certified copy of priority document

Document details: Country/Office: AU  
Number: 2003906117  
Filing date: 06 November 2003 (06.11.2003)

Date of receipt at the International Bureau: 01 December 2004 (01.12.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

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